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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/725,906	11/30/2000	Lisa McKerracher	06447-003-US-02	9776

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EXAMINER	
WEGERT, SANDRA L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/725,906	MCKERRACHER, LISA	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-21 and 23-52* is/are rejected.

7)☒ Claim(s) *22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2003* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/22/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.0.0

Detailed Action

Status of Application, Amendments, and/or Claims

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. This application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid.

The Amendment and Information Disclosure Statement, sent 22 November 2004, have been entered into the record. Claims 1-18 are cancelled. Claims 19-52 are new and read on the elected Invention.

Claims 19-52 are under examination in the Instant Application.

New/Maintained Claim Objections and/or Rejections

Claim Objections-

Claim 22 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections-35 USC § 112, first paragraph-scope of enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of Claims 11-18 for Scope of Enablement is *maintained* for reasons of record. This rejection was made in the previous Office Action at pages 3-5 (22 July 2004). Applicants canceled Claims 11-18 (22 November 2004). The Scope of Enablement rejection is maintained for newly-submitted claims. Applicant's arguments are sufficient to overcome the rejections based on "Rho antagonists."

Claims 19-21 and 23-52 are rejected under 35 U.S.C. 112, first paragraph, because the Specification, while being enabling for an axon-elongation stimulation kit comprising *C3* at tested concentrations (e.g., corresponding to a final *in situ* concentration of 25-50μg/ml), combined in a gel matrix with "fibrin sealant" (comprising fibrinogen concentrate, calcium chloride, thrombin and protease inhibitors), is not enabled for an axon-sprouting stimulation kit comprising any matrix-forming elements combined with C3 or similar proteins in at least one container, as described by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 19-21 and 23-52 are directed to an axon sprouting stimulation kit comprising two compartments (i.e., two syringe barrels separated by a valve or switch) for containing fibrin matrix-forming elements. The claims also state that at least one container comprises a therapeutically-active agent related to the C3 protein of *botulinum* toxin. The claims also describe a "mixing means" (i.e., a third barrel in which the matrix-forming elements are mixed before application). Dependent claims further list examples of C3-like molecules, and matrix-forming elements. However, the scope of the patent protection sought by the Applicant as

defined by the claims fails to correlate reasonably with the scope of enabling disclosure set forth in the specification for the following reasons:

The specification is not enabled for the full scope of the claimed kit, wherein the kit encompasses all "fibrin matrix-forming elements." Claims 21 and 36 recite, for example, "a component for cleaving fibrinogen," without listing the molecules described in the Specification that fall into this genus and are enabled, such as thrombin. Similarly, a "factor for catalyzing the cross-linkage of fibrin" as recited in Claim 23, is not enabled in its entire scope, because only a few such factors are described in the Specification (such as prothrombin), and it is not known if all such factors would function similarly in the claimed kit. Of the many anti-clotting factors found in nature, including the synthetic ones, different active mechanisms exist for each (see, for example recent reviews: Spronk, et al, 2004, Thrombosis J., 2: 12-21 and ten Berg, et al, 2001, Curr Control Trials Cardiovasc Med, 2: 129-140). Heparin and Triclopidine, for example act at different points in the clotting cycle. Conversely, fibrin can be polymerized by other molecules in addition to thrombin, but that does not necessarily indicate that other known factors can function like thrombin in isolation from blood (e.g., in the claimed kit). An important corollary issue here is that it is not known if the formation of the C3/fibrin matrix, by any means, is, by itself, sufficient for stimulating axon sprouting. Since so little is known in the art, or described in the Specification, about the relationship between the extracellular matrix and the axon growth cone, one has to be cautious about the extent of enabled subject matter in this case.

Furthermore, the instant Specification is not enabling for use of variants and truncated fragments of C3, as recited in Claims 20, 35 and 42. Specific substitutions in this enzyme may be enabled by the current literature (see for example: Saito, et al, 1995, FEBS, 371: 105-109).

However, since the art is primarily unpredictable and Applicants have not used a mutated or truncated form of C3 in their experiments, C3 with "one or more amino acids" substituted, removed or added is not enabled by the instant Disclosure.

Furthermore, the Specification is not enabling for use of all inhibitors of polysaccharide degradation, as recited in Claim 30. The instant Specification at page 30 suggests the use of flavenoids as inhibitors of polysaccharide degradation. In addition, several such inhibitors are known in the art for reducing scar formation in *superficial* experimental injuries (Blazso, et al, 2004, Phytother. Res., 18(7): 579-581). However, Applicants have not tested inhibitors of polysaccharide degradation in their experimental assays. Furthermore, it cannot be predicted from the current literature if such inhibitors would have expected effects on lesions in the central nervous system. For these reasons, it is not known which such inhibitors would function in a useful way in the claimed kit.

Similarly, the Specification is not enabling for use of all inhibitors of hyaluronic acid degradation, as recited in Claim 32. The instant Specification at page 30 suggests the use of inhibitors of hyaluronidase as inhibitors of hyaluronic acid degradation. In addition, such inhibitors are known in the art for decreasing contact inhibition in developing epithelial cells as well as in some cancer cells (Itano, et al, 2002, Proc. Natl. Acad. Sci., 99(6): 3609-3614). However, Applicants have not tested inhibitors of hyaluronic acid degradation in their experimental assays. Furthermore, it cannot be predicted from the current literature if such inhibitors would have expected effects on developing neurons in the central nervous system. For these reasons, it is not known which such inhibitors would function in a useful way in the claimed kit.

The specification discloses enabled utilities for an axon sprouting stimulation kit comprising the matrix forming elements fibrinogen, thrombin, protease inhibitors and $CaCl_2$, and C3-like molecules at tested concentrations (e.g., corresponding to a final *in situ* concentration of 25-50μg/ml). However, the instant claims read on a kit with multiple compartments comprising any combination of peptide or non-peptide compounds that are mixed with any thixotrope to form a fibrin matrix for facilitating axon sprouting.

Due to the large quantity of experimentation required to: a) determine how to use the kit described to stimulate axon sprouting, b) the lack of direction or guidance in the specification regarding same - e.g., the lack of guidance regarding use of components other than fibrin, fibrinogen, thrombin and $CaCl_2$, combined with C3 or Y-27632, c) the lack of working examples to all variants of the claimed components, d) the state of the art showing the many types of compounds that can stimulate or inhibit axon elongation, e) the unpredictability of function of encompassed compounds in terms of causing axon elongation, and f) the breadth of the claims which embrace innumerable compounds defined too broadly- undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

35 USC § 112, first paragraph – Written Description.

The rejection of Claims 11-18 for Written Description is *maintained* for reasons of record. This rejection was made in the previous Office Action at pages 3-5 (22 July 2004). Applicants canceled Claims 11-18 (22 November 2004). The Written Description rejection is maintained for newly-submitted claims.

Claims 19-21 and 23-52 are rejected under 35 USC § 112, as containing subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Claims 19-21 and 23-52 are directed to an axon sprouting stimulation kit comprising two or more compartments (i.e., two syringe barrels separated by a valve or switch) for containing *fibrin matrix-forming elements*. The claims also state that at least one container comprises a therapeutically-active agent related to the C3 protein of botulinum toxin. Claims 20, 35 and 42 encompass any *variant C3* polypeptide (e.g., with substitutions, deletions or insertions of *one or more* amino acids).

The specification teaches use of fibrinogen, thrombin, protease inhibitors and $CaCl_2$, and two C3-like molecules (C3 and Y-27632) at tested concentrations (e.g., corresponding to a final *in situ* concentration of 25-50μg/ml. However, the specification does not teach functional or structural characteristics of all claimed compounds. The description of several compounds described only as capable of "facilitating axon sprouting," "retaining ADP-ribosylation activity" "for cleaving fibrinogen," "for catalyzing the cross-linkage of fibrin" or of "forming a fibrin matrix" is not adequate written description of an entire genus of functionally equivalent compounds that stimulate axon sprouting or form a fibrin matrix. Similarly, Applicants were not in possession of clotting factors other than thrombin, catalysts other than $CaCl_2$, inhibitors of hyaluronic acid degradation or inhibitors of polysaccharide degradation.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the C3 and "fibrin matrix-forming" compounds referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed compounds, and therefore, would not know how to make or use them. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of making or using. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of use. *The product itself is required.* See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the kit comprising fibrinogen, thrombin, protease inhibitors and $CaCl_2$, and two C3-like molecules (C3 and Y-27632) at tested concentrations (e.g., corresponding to a final *in situ* concentration of 25-50μg/ml, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered

include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is a recitation of "facilitating axon sprouting," "retaining ADP-ribosylation activity" or "forming a fibrin matrix." There is not even identification of any particular portion of the C3 or matrix structures that must be conserved (for example, to maintain function). In the absence of a sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Making and using a representative number of variant C3 proteins or of different matrix-forming elements is likewise not adequately described.

Claim Rejections- 35 USC § 112, second paragraph - Indefiniteness

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claims 19-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for reciting or encompassing the phrase "container means." It is not clear from the Specification if this refers to a container or a means of performing a function. Since the invention as described in the Specification refers to a syringe-like apparatus, it is assumed that "container means" refers to a compartment or container. Modifying the phrase to read "compartment" or "container," for example, would be remedial.

Claims 19 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention. Claims 19 and 42 respectively list agents further comprising additions listed as Markush groups (see the last phrase of Claims 19 and 42), but then use neither "and" nor "or" before listing the final species in the list: "consisting of C3, Y-27632, Y-30141 for facilitating axon sprouting," and, "consisting of Y-27632, Y-30141, C3 protein." Substituting "and" before the last member of the phrase would be remedial.

Claims 20 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 20 and 35 contain the phrase "having an insertion in one or more amino acids and retaining." It is not clear from the claims or the Specification if this refers to substitution of an amino acid or other chemical species, or to modification of the existing residues. Modifying the phrase to read on amino acid substitution or amino acid modification would be remedial.

Additional References:

Ishizaki, et al, 2000, Mol. Pharmacol., 57: 976-983.

Winton, et al, 2002, J. Biol. Chem., 277(36): 32820-32829.

Taniguchi-Sidle, et al, 1992, J. Biol. Chem, 267(1): 635-643.

Itoh, et al, 1999, Nature Medicine, 5(2): 221-225.

Conclusion

Claims 19-21 and 23-52 are rejected. Claim 22 is objected to.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW
30 May 2005

JANET ANDRES
PRIMARY EXAMINER